IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No.:	10/748,524
Appellant(s):	Richard E. Parizek *et al.*
Confirmation No.:	8568
Filed:	December 29, 2003
Group Art Unit:	1645
Examiner:	Jana A. Hines
For:	A multicomponent vaccine containing clostridial and non-clostridial organisms in a low dose
Attorney Docket:	1995.184 US D1

November 12, 2008

REPLY BRIEF TO EXAMINER'S ANSWER

Mail Stop Appeal
Board of Patent Appeals
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir/Madam:

Pursuant to Appellants' April 18, 2008, Notice of Appeal, Appellants appeal all the claim rejections in the December 20, 2007, final Office action directed to the above-referenced patent application. Appellants submitted an Appeal Brief July 18, 2008. An Examiner's Answer was issued September 30, 2008. This Reply Brief is directed to issues raised by the Examiner that were either not particularly set forth in the rejections that are now on appeal or are questions raised for the first time regarding mathematical calculations presented by Appellants.

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II. STATUS OF CLAIMS (37 C.F.R. §41.37(c)(1)(iii))

A total of 48 claims have been introduced in this patent application. Claims 1-45 have been canceled. Thus, claims 46-48 remain pending. Every pending claim is rejected. This appeal requests reversal of all rejections.

III. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL (37 C.F.R. §41.37(c)(1)(vi))

Claims 46-48 have been rejected under 35 U.S.C. §103(a) for being obvious over Roberts (WO 94/22476) in view of Lund (U.S. Patent 3,920,811).

Claims 46-48 have been rejected under 35 U.S.C. §112, first paragraph, for not meeting the written description requirement.

IV. ARGUMENT

Roberts teaches against using depot (encapsulating) adjuvants

In the Examiner's Answer, the Examiner stated: "The CARBOPOL™ polymer adjuvant is a readily dispersible soluble adjuvant." Based on this assertion the Examiner concluded that the mention of CARBOPOL® by Roberts is "...a teaching of a different equivalent alternative, which achieves that same purpose of being an adjuvant in a method of immunization with a clostridial multicomponent vaccine is not a teaching away." (page 15, lines 4-8). Similarly, the Examiner stated "[i]t is agreed that Roberts teaches vaccines based on soluble adjuvants, and it is noted that no where is it taught that CARBOPOL™ is not a soluble adjuvant; and there is not teaching that depot adjuvants are not soluble adjuvants. Instead the Roberts and Lund references clearly polymer adjuvants, including CARBOPOL™, are known to readily absorb water and due to its hydrophilic nature; therefore the adjuvant is soluble. The instant specification at page 15, lines 22-28, state that polymers, including liposomes are adjuvants that function by encapsulating the antigen and releasing them over a period of weeks to months. Roberts and Lund teach administering compositions using water dispersible, water soluble adjuvants, contrary to Appellants' statements." (page 18, lines 9-18).

Contrary to the Examiner's assertion, CARBOPOL® and, generally, any "encapsulating polymer adjuvant" as recited in Appellants' claims, are not "readily dispersible soluble adjuvant[s]." They are not water soluble. When wet, they swell into hydrated spheres.

Roberts states:

> "Central to the present invention is the surprising discovery that stable, potent, multicomponent clostridial vaccines can be made **without the use of depot adjuvants**. In particular, the present invention provides for vaccines including rapidly dispersed, soluble adjuvants, that is, **adjuvants that are not retained at the injection site for a significant period of time, thereby exhibiting low tissue reactivity**. The vaccines can be administered intramuscularly and subcutaneously without the harmful side effects and chronic inflammatory responses that produce granulomas and abscesses, seen with other clostridial vaccine compositions when administered via these routes."

(emphasis added) (page 4, lines 24-32).

Roberts identifies CARBOPOL® as a depot adjuvant:

> "Clostridial toxoids are soluble proteins of relatively low antigenicity and, traditionally, poor stability. Thus, clostridial vaccines require adjuvants in order to increase antigenic potency and enhance stability. In particular, aluminum compounds, which are capable of adsorbing and/or precipitating clostridial toxoids, as well as retaining the toxoids at the injection site, are typically used. (References omitted). **Other potent depot adjuvants, such as** water-in-oil emulsions and **carbopol**, have also been used in clostridial vaccines." (emphasis added) (page 1, lines 33-38 and page 2, lines 1-2).

Roberts' invention consists of the discovery that injection site reactions experienced with depot adjuvants can be avoided by using adjuvants that are rapidly dispersed and soluble:

> "Central to the present invention is the surprising discovery that stable, potent, multicomponent clostridial vaccines can be made without the use of depot adjuvants. In particular, **the present invention provides for vaccines including rapidly dispersed, soluble adjuvants, that is, adjuvants that are not retained at the injection site for a significant period of time**, thereby exhibiting low tissue reactivity." (emphasis added) (page 4, lines 24-28).

The Examiner characterizes the use of depot adjuvants (Appellants' encapsulating polymer adjuvants) as a "less than optimal" alternative (page 11, line 4), as teaching a "different, equivalent alternative, which achieves that same purpose of being an adjuvant in a method of immunization with a clostridial multicomponent vaccine. Thus, solving the same problem with a functionally equivalent alternative is not a teaching away, as Appellants' urge. Furthermore, it is the Office's position that preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments." (page 13, lines 16-19).

As noted above, quoting Roberts, page 4, beginning line 24, "[c]entral to the

present invention [of Roberts] is the surprising discovery that stable, potent, multicomponent clostridial vaccines can be made without the use of depot adjuvants." (page 4, lines 24-26).

Roberts identifies CARBOPOL®, which is an example of Appellants' encapsulating polymer adjuvants, as a depot adjuvant. Use of such adjuvants is clearly taught against by Roberts:

> "Other potent **depot adjuvants, such as** water-in-oil emulsions and **carbopol**, have also been used in clostridial vaccines. **The above-described adjuvants**, although increasing antigenicity, **usually provoke severe persistent local reactions,** such as granulomas, abscesses and scarring, when injected subcutaneously or intramuscularly. **These local reactions are, in turn, responsible for carcass blemish which requires expensive trimming,** a consideration when the vaccine had been injected into muscle tissue destined to be a valuable cut of meat." (emphasis added) (page 2, lines 1-7).

The use of depot adjuvants, such as CARBOPOL®, is not a "functionally equivalent alternative" or a non-preferred embodiment. It is not a formulation that Roberts suggests is "less than optimal." It is specifically the type of composition that Roberts teaches should not be used.

> "A prior art reference may be considered to teach away when 'a person of ordinary skill, upon reading the reference, would be discourage from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.' In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). General skepticism of those in the art – not amounting to teaching away is also 'relevant and persuasive evidence' of nonobviousness. Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 726, 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). In effect, 'teaching away' is a more pointed and probative form of skepticism expressed in the prior art. In any case, the presence of either of these indicia gives insight into the question of obviousness." Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH. 139 F.3d 877,885, 45

USPQ2d 1977, 1984 (Fed. Cir. 1998)

CARBOPOL® polymer adjuvant is not a readily dispersible soluble adjuvant

On page 15, paragraph 2, the Examiner has stated a conclusion that CARBOPOL® is a readily dispersible soluble adjuvant. This statement is factually incorrect. Not only does Roberts define CARBOPOL® as a depot adjuvant that produces results Roberts is intending to avoid, the publicly available literature regarding CARBOPOL® reports that it is not water soluble. "The crosslinked polymers [CARBOLPOL®] are not actually water soluble, but swell into hydrated spheres that give the product its rheological properties." [Advance Mixing Technologies (ADMIX) (admix.com/carbopol.htm) (paragraph 3, page 1)] This is not a water dispersible, water soluble adjuvant. "The carbopol resins are hydrophilic substances that are not soluble in water. Rather, these polymers swell when dispersed in water forming a colloidal mucilage-like dispersion."["Carbopol, its Pharmaceutical Significance, a Review," (Pharmainfo.net)(lines 15-17)]. They are non-dispersible, not readily dispersible.

The Examiner uses impermissible hindsight

On page 16, the final paragraph, the Examiner uses impermissible hindsight to conclude that Roberts suggests that CARBOLPOL®, which the Examiner incorrectly characterizes as a "dispersible water soluble adjuvant," "...does not have inflammatory responses when administered in the 2ml dose and not the larger doses." The Examiner states: "This is further evidenced by Table 14 of Appellants' specification disclose that when comparing 2ml doses and 5ml doses of the same vaccine, the incidence of lesions was significantly reduced. Thus, one can only concluded that the reduction of lesion is from the use of a smaller dose, rather then the use of different adjuvants." (page 16, lines 16-20).

There is no statement or suggestion in Roberts regarding any dose size for vaccines comprising depot adjuvants. Appellants discovered that 2ml doses can be used without the side effects previously experienced using such depot adjuvants if the smaller

doses, such as 2ml doses, were used instead of conventional 5ml doses. Appellants' specification is the first disclosure of their discovery that lesions are reduced if smaller doses are used, yet protective immunity is achieved. Appellants respectfully submit that the Examiner has used impermissible hindsight, actually using data first presented in Appellants' specification, to support the Examiner's conclusion, as if it had been found in the reference.

Appellants' limitations are supported in the specification

Appellants include limitations in the claimed method of their invention based on their discovery that a reduced amount of vaccine, 2ml instead of the conventional 5ml, permitted the use of encapsulating polymer adjuvants that release antigens slowly at the site of injection, while overcoming the problems known in the art when using that kind of adjuvant; problems overcome by Roberts by using adjuvants having different physical characteristics. Appellants determined that injection site lesion formation is reduced at least 41% compared with 5ml injections of the same vaccine.

Support for the 41% reduction in injection site lesion formation is found, as acknowledged by the Examiner, in Table 12 on page 54, where the incidence of lesions in cattle at the time of weaning was reduced from 79.5% to 46.3%, this is a reduction of 41.76%, which supports the "at least 41%" limitation in Appellants' claims. The quantity of trim reported in Table 14 on page 55, it is believed, also supports the use of the "at least" term.

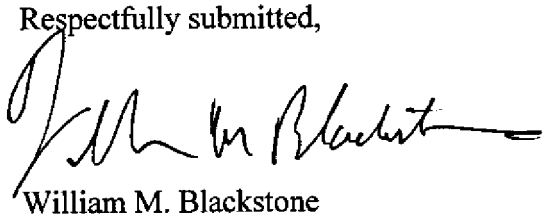
The Examiner is correct. Appellants, in error and without deceptive intent, identified Table 14 values of 69.4 and 30.3 as being percent reduction of lesions, when in fact theses figures refer to grams of trim necessary to remove injection site lesions. However, whether numerical incidents of lesion formation or quantity of wasted meat, the numerical results presented in Appellants' specification support the limitation of an injection site lesion formation reduction of at least 41% compared with an injection of 5ml of the same vaccine, as set forth in the claims now on appeal. Actual reduction in meat loss is (69.4 – 30.3)/69.4 or 56.3%.

Appellants respectfully point out, in addition, that the Examiner's statement, "...the reduction of the incidence of lesions after weaning is only 33.2% not at least 41% in Table 12," is incorrect. (page 21, lines 12 and 13) As noted above, the reduction in the incidence of lesions after weaning is 41.76%, a reduction from 79.5% for cattle vaccinated with 5.0ml of the vaccine, reduced to 46.3% for cattle vaccinated with 2.0ml of the vaccine. That is, Table 12 on page 54 reports that with 5.0ml of vaccine, 31 of 39 animals developed injection site lesions (79.5%) and with a 2ml vaccination only 19 of 41 animals developed injection site lesions (46.3%). The reduction from 79.5% to 46.3% is a reduction of (79.5%-46.3%)/79.5% or 41.76%. These results are set forth plainly in the tables accompanying Example 8 in Appellants' specification. No new matter was introduced in the amendments incorporating these limitations in Appellants' claims.

V. Fee payment

Appellant does not believe that any other fee is due in connection with this filing. If, however, Appellant does owe any such fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit Account No. **02-2334**. In addition, if there is ever any other fee deficiency or overpayment in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **02-2334**.

Respectfully submitted,



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